Early, goal-directed resuscitation for septic shock

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Abstract: The Protocolised Management in Sepsis (ProMISe) trial (April 2 issue) completes a trio of studies that question the further application of early, goal-directed therapy (EGDT) as suggested by Rivers et al. In particular, these trials consistently show no survival benefit with regard to the mandated use of central venous oxygen saturation ($ScvO_2$) monitoring. However, it remains questionable whether the results of the three trials support this claim. According to the EGDT protocol, an $ScvO_2$ value of less than 70% is a trigger for hemodynamic intervention. Unlike in the study by Rivers et al., the reported mean values at baseline in all three trials do not require any intervention. Whether the reported survival benefit in the study by Rivers et al. is based on the treatment of patients with initially extremely low $ScvO_2$ values and determines the targeted patient population that benefits from EGDT remains, therefore, unanswered. Pope et al. reported increased mortality when $ScvO_2$ values were initially low (<70%) or high (>80%). Unless subgroup analyses and further studies that focus on these high-risk patients do not rule out a survival benefit, the final conclusion of the three trials cannot be supported.

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CORRESPONDENCE

Early, Goal-Directed Resuscitation for Septic Shock

TO THE EDITOR: The Protocolised Management in Sepsis (ProMISe) trial (April 2 issue)[1] completes a trio of studies[1-3] that question the further application of early, goal-directed therapy (EGDT) as suggested by Rivers et al.[4] In particular, these trials consistently show no survival benefit with regard to the mandated use of central venous oxygen saturation ($ScvO_2$) monitoring. However, it remains questionable whether the results of the three trials support this claim. According to the EGDT protocol, an $ScvO_2$ value of less than 70% is a trigger for hemodynamic intervention. Unlike in the study by Rivers et al., the reported mean values at baseline in all three trials do not require any intervention. Whether the reported survival benefit in the study by Rivers et al. is based on the treatment of patients with initially extremely low $ScvO_2$ values and determines the targeted patient population that benefits from EGDT remains, therefore, unanswered. Pope et al.[5] reported increased mortality when $ScvO_2$ values were initially low (<70%) or high (>80%). Unless subgroup analyses and further studies that focus on these high-risk patients do not rule out a survival benefit, the final conclusion of the three trials cannot be supported.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The ProMISe trial investigators report that EGDT did not reduce 90-day mortality among patients with early septic shock. Fluid therapy is crucial in EGDT. By 72 hours, approximately 40% of the study patients had received a median of 1.0 liter of intravenous colloids, and 98% of the patients had received a median of 4.9 liters of intravenous crystalloids (Table S7 in the Supplementary Appendix of the article, available with the full text of the article at NEJM.org). The values for the interquartile range indicate that individual patients had received considerably larger amounts. Similar amounts of fluids in the treatment of early septic shock have been shown to increase mean serum chloride concentrations from 100 mmol per liter initially to 106 to 108

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mmol per liter during the first 72 hours,[1] probably related to the use of hyperchloremic solutions. Such solutions are well known to be associated with numerous adverse outcomes.[2,3] Red-cell transfusion is also associated with worse outcomes, including those in critically ill patients.[4] Because the use of hyperchloremic solutions and blood transfusions might have obscured potential treatment effects, information regarding types of fluids, serum chloride concentrations, and the reason for the significantly higher frequency of red-cell transfusions in the EGDT group than in the usual-care group is required.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The ProMISe trial, the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial, and the Protocolized Care for Early Septic Shock (ProCESS) trial suggest no additional benefit from hemodynamic management with strict EGDT, characterizing EGDT only as a hemodynamic study. In addition to hemodynamic monitoring from the EGDT component, the Surviving Sepsis Campaign (SSC) guidelines[1] include early detection of high-risk patients with the use of the criteria of the systemic inflammatory response syndrome, the shock index (ratio of heart rate to systolic blood pressure), and measurement of serum lactate levels. EGDT has played a central role in the development of current tenets of shock management. In the triad of randomized, controlled trials, each component of EGDT was applied in all groups except monitoring of central venous pressure and $ScvO_2$, and they were provided in more than 50% of the participants in the usual-care groups. Mortality decreased in both control and intervention groups by more than 50% — a greater degree than in previous trials. These results strongly support the pivotal role of the SSC guidelines that include EGDT.[1-3] Although these trials reveal that monitoring of central venous pressure is not mandatory, they show no harm in EGDT and certainly do not suggest that other aspects of the guidelines be called into question. We are concerned that the conclusions promulgated by the triad of trials will be misinterpreted and will cast doubt on the importance of SSC protocols for sepsis detection and treatment.

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Drs. Claypool and Manaktala report being paid employees of Wolters Kluwer Health, which provides decision support for sepsis. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Auinger and Maggiorini suggest that the ProCESS,[1] ARISE,[2] and ProMISe trials reported mean $ScvO_2$ values at baseline that are considerably higher than those in both the EGDT group and the usual-care group in the study by Rivers et al.[3] The values to which they refer for the EGDT groups in the three trials, however, are not baseline values and are typically from at least 1 hour postrandomization (after insertion of the catheter with $ScvO_2$ monitoring capability). The values in the study by Rivers et al. are prerandomization (all patients received catheters with $ScvO_2$ monitoring capability before randomization in this study), and, therefore, the comparison is not valid. Subgroup analyses of high-risk patients in the three multicenter trials, using illness-severity scores, serum lactate concentrations, or both as proxies for baseline

$ScvO_2$ (because $ScvO_2$ data were not available for the usual-care groups), showed no evidence of benefit.

We agree with Priebe that administration of intravenous isotonic saline solutions can cause hyperchloremia and acidosis. In the ProMISe trial, although we did not record the type of crystalloid administered or the serum chloride level, the volume of crystalloid administered by 72 hours after randomization was similar in the EGDT and usual-care groups, and it is likely that, on average, the fluids used were the same in the two groups. With respect to red-cell transfusions, the evidence base is conflicting, with more recent data[4,5] indicating no evidence of harm caused by transfusions.

Manaktala and Claypool are concerned about misinterpretation of the results of the ProCESS, ARISE, and ProMISe trials. With interpretation in mind, we stated in the Conclusions section of the abstract of our article that "in patients with septic shock who were identified early and received intravenous antibiotics and adequate fluid resuscitation, hemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome."

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Since publication of their article, the authors report no further potential conflict of interest.

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Rociletinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer

TO THE EDITOR: Sequist et al. (April 30 issue)[1] report that rociletinib can overcome the resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in patients with non–small-cell lung cancer (NSCLC) harboring the *EGFR* T790M resistance mutation. Rociletinib treatment was associated with significantly longer progression-free survival among such patients than among patients not harboring these mutations. We noted that of the 92 study patients who received therapeutic doses of rociletinib, 35 (38%) also received glucose-lowering therapy (typically metformin) to treat hyperglycemia.

Metformin, an antidiabetic drug, has been shown to exert anticancer activity. Lin et al. reported that metformin administration is associated with improved survival among patients with stage IV NSCLC with diabetes.[2] Our study showed that metformin sensitizes NSCLC cells that are resistant to EGFR tyrosine kinase inhibitors.[3] Furthermore, metformin suppresses the expression of the main detoxification enzyme, cytochrome P-450 3A4.[4] Therefore, it could theoretically elevate plasma concentrations of rociletinib. These effects raise the possibility that metformin may have affected the results of the study by Sequist et al. I would like to know whether the patients who received rociletinib and metformin had better outcomes than those who received rociletinib only.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We agree that some evidence suggests that metformin has intrinsic anticancer